FROM WALTER B. ESSMAN,M.D.,Ph.D.
Re Grant Application #905
May 21, 1973

RESEARCH PROPOSAL EVALUATION
Dr. Edward F. Domino
Neuropsychopharmacological Effects of Chronic Nicotine

The behavioral studies proposed for this investigation are not impressive and raise several questions regarding their over-all significance to the tissue studies proposed in the later section of the proposal. It is further noted that the behavioral techniques utilized have little relationship to one another, so that it is difficult, if not impossible, to make statements about shuttle-box avoidance that might be relatable in any respect to positively reinforced operant responses, electric self-stimulation or waking sleep cycles. It would be more appropriate, perhaps, to design such experiments using quantitatively low, high activity labeled nicotine, in conjunction with cold-loading doses, so that the time course of behavioral changes can be more meaningfully related to what now seems to be relatively independent experiments in the second portion of the proposal. The same comment might be made with regard to Experiment 3, which might, perhaps, be more appropriately be undertaken as the initial experiment in this proposal.

Insofar as Experiment 4 is concerned, there are a number of methodological problems which might be pointed to. Microwave irradiation as a method of sacrificing mice or for achieving rapid fixation of tissue is a highly unsatisfactory technique when applied to a consideration of the cholinergic system. Its efficiency is by no means comparable to that of Near-freeze methods, nor does it provide for a very satisfactory procedure if discrete tissue morphology

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is to be retained. With regard to the latter, the investigator does not specify which region or regions of the brain he proposes to re-examine in rodents or whether his study has been designed for whole brain assessment of cholinergic changes for nicotine treatment.

The investigator does not clearly point out that the investigations of Homestead and Lundgren were carried out in rats, not mice, utilized whole brain assays and were treated with physostigmine salicylate, in order to preclude enzomatic hydrolysis. The total acetylcholine levels measured in this study were only obtained within the first 10 minutes following the injection of an inordinately large dose of nicotine barbiturate and it might be pointed out that there is no data available for times beyond 10 minutes.

The studies reported by Essman were carried out in the mouce and referred only to the tissue of the cerebral cortex which were measured 45 minutes following administration of nicotine sulphate, following which, changes in several storage pools of this amine were measured. A comparison of the different results from these two sets of experiments hardly seem to generate any area of controversy through which definitive further studies are going to settle any issue.

The final experiment proposed in section 5 seems completely unrelated to those studies which are outlined in previous sections of the proposal, and there is no indication of what significance these would have.

I certainly believe that the investigator is a highly competent, established researcher, but the proposal is in general disappointing, in that I find very little that would essentially contribute either new methodology or empirical data for behavioral, biochemical or electrophysiological research of nicotine pharmacology. I think that the author probably has more to say about the scope

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of his proposed research than he has outlined in the proposal, and I would hope that he does limit the scope of the proposed investigation and also clarify several of the issues presented within such a limited scope.

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